IMMUNOLOGY

IgA Deficiency: Clinical Correlates with IgG Subclass and Mannan-binding Lectin Deficiencies

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Objective. **To characterize an IgA deficient population in terms of the incidence of IgG subclass and mannose-binding lectin (MBL) deficiencies and the type and severity of infections and other associated disorders.**

Background. **Selective IgA deficiency is probably the commonest of the primary immunodeficiency disorders and although it may lead to an increased risk for respiratory and gastrointestinal infections and associated to various autoimmune diseases, it may also be asymptomatic. Several studies have suggested the need of a concomitant defect in order for manifestation of its symptoms.**

Methods. **A total of 27 patients fulfilling the diagnostic criteria of selective IgA deficiency were evaluated for IgG subclass and MBL deficiencies after a thorough medical history, physical examination and pertinent evaluation for concomitant medical conditions.**

Results. **The overall incidence of IgG subclass deficiency found in the IgA deficient group was 18.5%. MBL deficiency was found to be 3.7%. These frequencies may have been influenced by the age group evaluated and the size of the population studied. Severe infections were more common in patients with combined deficiencies. either IgA and any of the IgG subclasses or IgA and MBL deficiency. Atopy was widely represented in the patients studied.**

Conclusions. **The observed relationship between combined deficiencies Ig A, IgG subclasses and MBL and the increased representation of severe infections needs to be corroborated in a larger sample of patients with an inclusion of pediatric patients.**

Key words: Selective IgA deficiency, IgG subclass deficiencies, Mannose-binding lectin deficiency, Infections

IgA deficiency has been categorized as the most common of the primary immunodeficiencies, usually associated with increased susceptibility to infection although, some patients are asymptomatic (1). Its frequency is estimated to be between 1 in 400 and 1 in 2000 persons in the general population. This deficiency is thought to be the result of a terminal B cell differentiation disorder that is linked to the HLA-DQ/DR locus and an extended major histocompatibility complex (MHC) haplotype (HLA-B8, SCOI, DR3) (2). IgA deficiency is a heterogeneous condition whose symptomatology may include respiratory or gastrointestinal manifestations, atopy, asthma and a myriad of inflammatory/autoimmune diseases, like systemic lupus erythematosus, ulcerative colitis, Crohn's, rheumatoid arthritis and pernicious anemia, among others.

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It has been suggested that IgA deficiency requires an association to an IgG subclass deficiency, especially IgG2 and IgG4, for its participation in severe infectious processes. The association of IgG 1 with several primary or secondary immunodeficiency states, the relation of IgG2 to polysaccharide antibodies and the identification of IgG3 with some autoimmune conditions have all been previously reported, however an isolated IgG4 deficiency has not been convincingly demonstrated (3). On the other hand, mannan-binding lectin (MBL) deficiency has been related to IgG subclass deficiency in pediatric patients with increased susceptibility to infections (4). Mannose-binding lectin is a collagenous serum protein of hepatic origin that forms part of the innate immune system. MBL is able to bind through multiple sites to carbohydrate structures in certain bacterial surfaces, leading to complement activation, thus making bacteria more susceptible to phagocytosis. (5). Reduced serum concentrations of MBL are associated to SLE (6). Recent investigations have suggested a role of MBL in the clearance of atherogenic particles (7).

The aim of this study was the determination of the clinical and laboratory characteristics of lgA deficient

patients followed at our Immunology Clinic, specifically in terms of infectious manifestations and IgG subclass and MBL levels.

Methods

Study patients. The study group comprised patients referred to the Immunology Clinic of the University Hospital by their primary physicians for evaluation of recurrent infectious episodes and/or other medical conditions. In addition, two asymptomatic patients who were identified during a blood donor screening activity were subsequently evaluated and included in the study group. A total of 27 patients were studied over a period of ten years. Initially, every patient underwent a complete history, physical examination and baseline laboratory tests through a uniform protocol. For inclusion in the study, the patients had to be 20 years or older, be able to complete the evaluation forms, have the capacity to give informed consent and agree to comply with the sample drawing schedule.

Immunological parameters. All patients were confirmed to have IgA deficiency by analysis of their IgA levels on two fresh serum samples analyzed in separate reference laboratories. The methodology used was immunoturbidimetry and IgA deficiency was defined as an IgA level less than or equal to 10 mg/dL. IgG, IgM and IgE levels were assayed using the same methodology. IgG subclasses (1 to 4) were measured by nephelometry. The patients had two samples taken at three month-intervals for assurance of reliability of the measured parameters, in view of reported variations in normal IgG subclass levels (8). MBL levels were examined by enzyme immunoassay (EIA) at a reference laboratory. The reference values for IgG subclass levels and MBL levels are addressed to in the results section of this article. Any inflammatory or autoimmune condition present in the patient population was diagnosed by standard criteria. Infections were corroborated through clinical, X-rays and/or cultures parameters, as indicated.

Statistical analysis. An average of the two samples of the IgG subclass values was used to assess the incidence of deficiencies. The median and the percentage distribution of the IgG subclass levels were calculated.

Table 1. Clinical Associations of IgA Deficient Population

Condition	Number of patients (n= 27)
Recurrent infections	25 (92.5%)
Atopy	13 (48.1%)
Autoimmune disorders*	7 (25.9%)
Asymptomatic	2 (7.4%)

*Ulcerative colitis 3; Crohn's disease 2; SLE 2

Results

The profile of IgA deficient patients included 17 men and 10 women between the ages of 20 and 57 years. As shown in Table 1, the most common clinical presentation observed were recurrent infections (92.5%) followed by atopy/asthma (48.1 %).

Table 2 includes a detailed account of the infectious episodes identified. Viral respiratory infections constituted the commonest manifestation, followed by bacterial respiratory infections. Severe infections were identified as: infections requiring antibiotics and/or associated to morbidity.

Table 2. Infections in IgA Deficient Group

Condition	Number of patients (%) (n=27)
Viral respiratory infections	25 (92.5%)
Bacterial respiratory infections	4 (14.8%)
Urinary tract infections	3 (11.1 %)
Bronchopneumonia	2 (7.4%)
Sepsis	1 (3.7%)
Giardiasis	1 (3.7%)

Table 3. Clinical Manifestations and Alterations in IgG Subclass Levels Observed in IgA Deficient Population (n = 27)

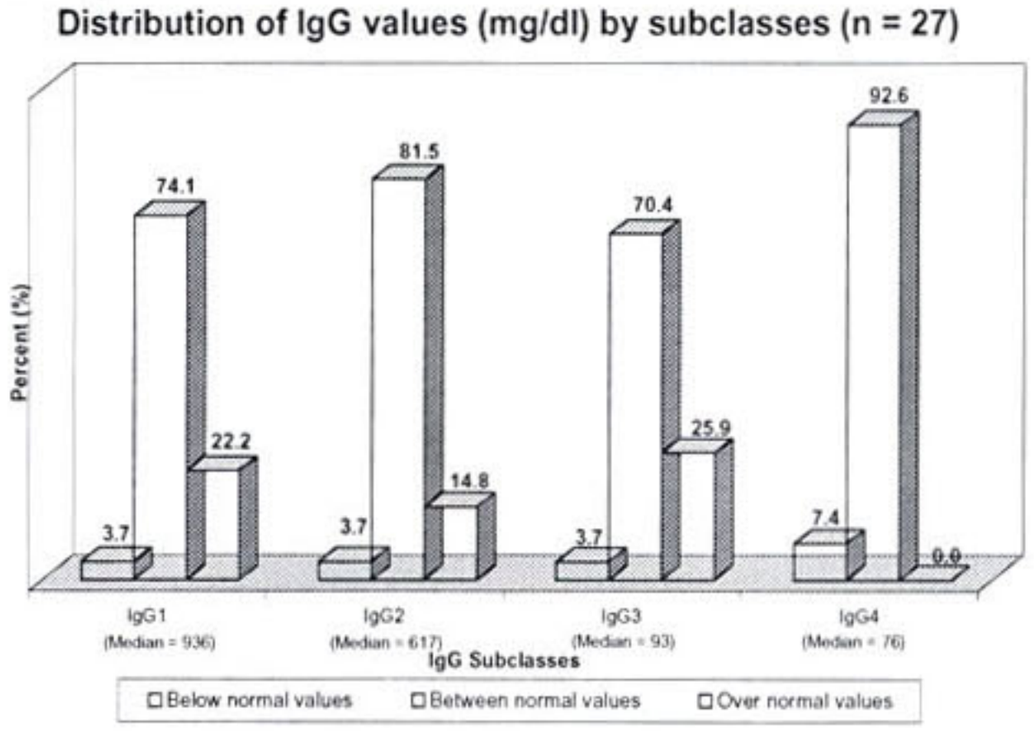
Patient	Deficiency	Manifestations
1	IgA, IgG4	BKP; UTI; VRI; Allergies
2	IgA	Giardia; UC; VRI
3	IgA	VRI; Allergies; Asthma
4	IgA	Crohn's; VRI; Allergies
5	IgA, IgG2	BKP (pneumococcus); VRI
6	IgA	VRI; Allergies
7	IgA, High IgG1, IgG2, IgG3	Asymptomatic
8	IgA	VRI
9	IgA	VRI; Allergies; Asthma
10	IgA	VRI
11	IgA, MBL	SLE; UTI; BRI; VRI
12	IgA	Crohn's; VRI
13	IgA	VRI; Allergies
14	IgA	UC; VRI
15	IgA, High IgG1, IgG2, IgG3	Asymptomatic
16	IgA	VRI; Allergies; Asthma
17	IgA	VRI
18	IgA	VRI
19	IgA, IgG4	UTI; BRI; Allergies; VRI
20	IgA	VRI; Allergies; Asthma
21	IgA, High IgG1, IgG2, IgG3	VRI; Allergies
22	IgA, IgG3	SLE; BRI; VRI
23	IgA, High IgG1	VRI; Allergies
24	IgA, IgG1	BRI; sepsis; CVI; VRI
25	IgA	VRI; Allergies; Asthma
26	IgA, High IgG1, IgG2, IgG3	UC; VRI
27	IgA	VRI; Allergies

Abbreviations:
BKP = bronchopneumonia SLE = systemic lupus erythematosus
UTI = urinary tract infections BRI = bacterial respiratory infections
VRI = viral respiratory infections CVI = common variable immunodeficiency
UC = ulcerative colitis

The associations between IgA deficiency and IgG subclass alterations are illustrated in Table 3. The overall incidence of IgG subclass deficiency in the study group was 18.5% (5 patients) and that of MBL deficiency was 3.7% (1 patient). As shown in this table, 2 patients with IgG4 deficiency had severe infections and allergies; 1 patient with IgG3 deficiency had SLE and another had MBL deficiency; 1 patient with low IgG2 had pneumococcal pneumonia; 1 patient with low IgG 1 had Epstein-Barr virus infection and sepsis and later developed common variable immunodeficiency after nine years of observation. Two asymptomatic patients had elevated IgG 1, IgG2 and IgG3 levels. The incidence of atopy in this population was 48.1% and no patient demonstrated IgE deficiency.

Figure 1 contains the distribution of IgG subclass levels of the study group, with the indication of the median values for each of the subclass levels.

Figure 1. Distribution of IgG Subclass Levels of the Study Group



Discussion

The increased susceptibility to infections in some individuals with IgA deficiency is probably not related to IgA deficiency alone. Although based on a limited number of cases, the present study relates lower serum concentrations of IgG2 and IgG4 with the presence of the more severe infections observed. Some studies have identified lower mean concentrations of IgG subclasses in IgA deficient patients with an increased susceptibility to infections, although this finding has not led to a clear association in all cases. (9). That discrepancy might be explained by the fact that the populations studied in different series have been variable in size, that the assays utilized to determine the IgG subclass levels have been different and not repeated and that the identification of infectious processes has not followed a uniform procedure. Some authors have suggested that a correlation of specific antibody titers, like pneumococcal antibodies, might be a better indicator in assessing the relation between infections in IgA deficient patients with concomitant IgG subclass deficiencies (10, 11). It is noteworthy that two of the four patients with elevated IgG 1, IgG2 and IgG3 subclass levels in the studied population were asymptomatic, a finding which is in concordance with the results of other studies in the literature (12).

As only one patient with MBL deficiency was identified in our study no valid statement can be made regarding the combined presence of IgA and MBL deficiency. Interestingly enough, this patient had SLE and presented with recurrent urinary tract infections as well as bacterial respiratory infections.

The exclusion of patients in the pediatric age group in our study could have been a factor contributing for not identifying other cases of MBL deficiency in our sample. The overall occurrence of IgG subclass deficiency and of MBL deficiency in this study was probably influenced by the sample size and the age group studied. Of interest in our sample was the association of IgG 1 subclass deficiency and the IgA deficiency and the subsequent development of common variable immunodeficiency in one of our patients. That case initially presented with an Epstein-Barr virus infection, subsequent sepsis. An antibody screening revealed the combined deficiency.

As mentioned in other publications in some IgA deficient individuals, the terminal B cell differentiation disorder may include additional abnormalities of antibody-mediated immunity, including IgE deficiency (13). In this study no patient was identified with IgE deficiency. A strong association between IgA deficiency and atopy was observed despite normal IgE levels as reported in other series (14). A continued surveillance of these patients is required to assess whether the observed tendencies persist.

Resumen

El objetivo de este estudio fue hacer un análisis y caracterización de un grupo de pacientes con deficiencia de la inmunoglobulina A en términos de deficiencias asociadas en subclases de la inmunoglobulina G y de la lectina enlazada a la manosa ("MBL", por sus siglas en inglés), así como de la incidencia y severidad de infecciones y otros desórdenes clínicos en esta población. Se evaluó una muestra de 27 pacientes adultos entre las edades de 20 a 57 años que cumplieron con los criterios diagnósticos para una deficiencia selectiva de IgA, los cuales también fueron evaluados para la detección de deficiencias de subclases de IgG y la lectina ligada a

manosa. Todos los pacientes fueron sometidos a historiales y exploraciones fisicas detalladas así como a las evaluaciones de laboratorio y los procedimientos indicados para la detección de desórdenes clínicos concurrentes. La incidencia de deficiencias de subclases de la inmunoglobulina G fue de 18.5%. La deficiencia de lectina fue de 3.7%. Se encontró que las infecciones severas ocurrieron más frecuentemente en pacientes con deficiencias combinadas de IgA con subclases de IgG o con lectina ligada a manosa. Se postula que las frecuencias observadas pudieran haber estado relacionadas al grupo de edad examinado. La relación demostrada entre una deficiencia combinada de inmunoglobulina A, las subclases de IgG y la lectina ligada a manosa y una mayor incidencia de infecciones severas requiere su corroboración mediante el examen de una muestra más significativa de pacientes y probablemente la inclusión de pacientes en edades pediátricas.

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